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Influence of Clinical and Demographic Variables on Mycophenolic Acid Pharmacokinetics in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Abstract

Background—Mycophenolic acid (MPA) is used off-label to treat many forms of glomerulonephritis.

Objective—To evaluate the pharmacokinetics of MPA and its glucuronide (MPAG) in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis patients with renal manifestations and to determine the effects of clinical (urinary protein excretion, serum albumin, creatinine clearance) and demographic (age, race, sex) variables on MPA and MPAG pharmacokinetics.

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The University of North Carolina has received funding from Roche to conduct clinical studies with methoxy polyethylene glycol-epoetin beta. Dr. Joy was the institution's principal investigator of those studies.

Methods—Twenty-three patients taking MPA at steady-state were evaluated. Plasma and urine samples were collected over 24 hours. Analyses included noncompartmental pharmacokinetics and statistics including Mann-Whitney *U* test and univariate/multiple regression.

Results—MPA clearance (Cl/F 288 ± 154 mL/min) was approximately 2-fold higher than previously reported from transplant patients and predicted by weight and race (ranked MPA $Cl/F = -11.766 + 0.2035 [wt] + 4.9578 [race]$; R^2 41.8%; $p = 0.005$). Creatinine clearance ($CrCl$) less than 60 mL/min resulted in higher MPA exposure, total area under the curve (AUC)₀₋₁₂, and AUC ₆₋₁₂, as well as unbound AUC ₀₋₁₂. The metabolic ratio ($MPAG_{AUC}/MPA_{AUC}$) of 8.67 ± 5.57 was lower than that previously reported in renal transplant recipients.

Conclusions—Diminished kidney function (eg, $CrCl < 60$ mL/min) demonstrated enhanced MPA and MPAG exposure in patients with ANCA vasculitis. However, unlike renal transplant recipients, patients with ANCA vasculitis had enhanced Cl/F and diminished metabolic ratio, suggesting the need to comprehensively evaluate the role of disease-specific factors on MPA pharmacokinetics.

Keywords

antineutrophil cytoplasmic antibody–associated vasculitis; individualized therapy; mycophenolic acid; pharmacokinetics

Mycophenolic acid (MPA) is used off-label for treatment of immune-mediated disorders and is approved by the Food and Drug Administration (FDA) for prevention of transplant rejection.¹⁻⁶ Three studies evaluated the efficacy of MPA in small-vessel vasculitis.⁷⁻⁹ In one of these, we reported 3-fold improvements in disease activity (Birmingham Vasculitis Activity Score) in patients experiencing disease relapse compared with those defined as treatment resistant. While patients with kidney manifestations of vasculitis are similar to renal transplant recipients in that they can have alterations in glomerular filtration rate, they also often have altered serum albumin, urinary protein, and markers of inflammation.

Since interindividual variability in MPA pharmacokinetics has been documented in transplant recipients, therapeutic plasma monitoring has been suggested to improve immunosuppressive outcomes.¹⁰⁻¹³ Area under the plasma concentration–time curve from 0 to 12 hours (AUC ₀₋₁₂) of 30–60 mg•h/L and trough plasma concentrations of 1–3.5 mg/L were suggested as targets for triple combination immunosuppressive therapy in kidney and heart transplant patients.^{13,14} Target ranges for MPA in autoimmune kidney diseases, such as lupus nephritis and antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, have not been established.

The primary purpose of this study was to evaluate the pharmacokinetics of total and unbound MPA and its metabolite, phenolic *O*-glucuronide (MPAG), in ANCA vasculitis. The secondary objectives were to determine the effects of clinical parameters (urinary protein to creatinine excretion ratio [UP:Cr], serum albumin, creatinine clearance [$CrCl$]) and demographic variables (age, race, sex) on pharmacokinetics of the drug and its metabolite.

Methods

Patients

Patients with biopsy-confirmed ANCA vasculitis receiving MPA therapy (as mycophenolate mofetil) and at steady-state were eligible. Concomitant therapies with other immunosuppressants were permitted and recorded. Patients entered the institution's general clinical research unit for 24 hours for assessment of the pharmacokinetics of MPA at the dose and interval that was prescribed. Patients were fasting at study initiation and were then fed a standard diet. $CrCl$ (calculated by the Cockcroft-Gault equation¹⁵), UP:Cr, serum albumin, and

serum creatinine were obtained/recorded. The study was approved by the university's Institutional Review Board in accordance with the Declaration of Helsinki.

Pharmacokinetic Study

After baseline blood samples were obtained for measurement of a trough plasma concentration (Ctr), patients were instructed to take their morning dose of MPA. Plasma samples (7.5 mL) were obtained at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours, immediately centrifuged for 10 minutes at 4 °C, aliquoted, transferred to plastic screw-top tubes, and stored at -80 °C until assay. Urine was collected at intervals of 0–6, 6–12, and 12–24 hours into acidified (15 mL 6 N HCl) collection containers; volumes were recorded and 2-mL aliquots were stored at -80 °C until assay. Plasma and urine samples were processed and assayed as described previously.^{16,17} Unbound plasma fraction was determined as previously described.¹⁷ Plasma and urine standard curves for MPA were linear over the ranges of 0.2–200 and 1–50 mg/L, respectively. Plasma and urine standard curves for MPAG were linear over the ranges of 1–200 and 5–1500 mg/L, respectively. MPAG concentrations were represented in terms of MPA equivalents by multiplying the MPAG concentration by 0.646 (molecular mass of MPA to MPAG) and are reported in milligrams per liter. The amount of MPA available from a dose of mycophenolate mofetil was estimated as 72% of the dose.

Pharmacokinetic Analysis

Noncompartmental pharmacokinetic analysis of total and unbound MPA and total MPAG was conducted using WinNonlin v4.1 (Pharsight, Mountain View, CA). Maximum concentration (C_{max}), time to C_{max} (t_{max}), Ctr at 12 hours, AUC_{0-12} , oral clearance (Cl/F), renal clearance (Clr), and mean residence time (MRT) were recorded. Both concentration and AUC parameters were dose-normalized, and the clearance data were adjusted to a 70-kg patient based on a scaling method, using a power of 0.75.¹⁸ We made the assumption that bioavailability (F) was equal to 1, as reported previously.¹¹ AUC_{12-24} and AUC_{6-12} were calculated, and the latter was used to estimate apparent enterohepatic recycling.^{19,20} Amount of MPA and MPAG in urine over each collection was determined by multiplying concentration by volume. MPA and MPAG amounts in urine (Ae) were computed for 0–12 hours by adding the Ae for the first 2 intervals. Clr for the 0- to 12-hour time was calculated by Ae_{0-12}/AUC_{0-12} .

Statistics

Descriptive analyses for pharmacokinetic and demographic variables and laboratories included means, standard deviations, and medians, as appropriate. Bivariate assessments of the key characteristics (serum albumin, UP:Cr, CrCl, age, weight, race, prednisone dose) versus each pharmacokinetic parameter of interest (MPA Cl/F, AUC_{0-12} , AUC_{6-12} , Ctr₁₂, Clr, Cl_{unb} , and $AUC_{unb 0-12}$; as well as MPAG AUC_{0-12} and Clr) were assessed by Spearman rank correlations. The effect of cyclosporine on MPA could not be directly assessed, because only 3 patients were receiving the drug. The correlations and resultant p values from the bivariate assessments were analyzed for possible inclusion into multiple regression models that predicted pharmacokinetic parameters. Correlations with a p value less than 0.15 were selected for incorporation into the multiple regression models. Variables were transformed to ensure that each followed a normal distribution. Model building for analysis of determinants of the parameters identified above consisted of multiple linear regression analysis with forward addition of variables as well as backward elimination, noting influences on the coefficients of the primary predictors. The final model was selected based on significance of each variable on predicting the parameters in the model, as well as the overall R^2 of the model.

Comparison between clinical groups based on CrCl (<60 vs ≥60 mL/min) and UP:Cr (<500 vs ≥500) was analyzed by nonparametric Mann-Whitney *U* test. It was not possible to compare

serum albumin groups, as there were no significant deviations from the laboratory's reference range.

Results

Twenty-three patients with biopsy-confirmed ANCA small-vessel vasculitis completed the MPA/MPAG pharmacokinetics study. Patient demographics included age 53 ± 14 years, 57% female, 78% white, and weight 87 ± 19 kg. Nonwhite races consisted of African American ($n = 3$), Asian ($n = 1$), and other ($n = 1$). All patients were receiving the mycophenolate mofetil prodrug of MPA, with the exception of one patient (prescribed mycophenolate sodium), who was included in the analyses, as the pharmacokinetics were similar. The average MPA daily dose was 1489 ± 596 mg with dosing divided twice daily in all but one patient, who was dosed once daily. The distribution of doses was 250 mg ($n = 1$), 500 mg ($n = 9$), 750 mg ($n = 4$), 1000 mg ($n = 8$), and 1500 mg ($n = 1$). Clinical laboratory results were serum creatinine 1.3 ± 0.6 mg/dL (range 0.7–3.4), UP:Cr 0.42 ± 0.50 (range 0.04–1.87), CrCl 84.4 ± 40.1 mL/min (range 18.3–182.2), and serum albumin 4.4 ± 0.40 g/dL (range 3.6–5.2). Thirty percent ($n = 7$) of the patients were receiving concomitant glucocorticoids and 13% ($n = 3$) were receiving cyclosporine.

MPA Pharmacokinetics

A concentration versus time profile for one patient at steady-state MPA and MPAG concentrations over 12 hours is presented in Figure 1. The mean pharmacokinetic parameters for patients with ANCA vasculitis are provided in Table 1. The scaled Cl/F of 288 ± 154 mL/min suggests that MPA is a moderate extraction ratio drug whose metabolism could be impacted by changes in unbound fraction. The mean percentage of unbound MPA was $1.0 \pm 0.6\%$, with all patients having unbound fractions of 2.4% or less, similar to the expected unbound fraction.^{11,21} The MPA AUC₀₋₁₂ was outside the 30- to 60-mg•h/L range that was recommended in kidney transplant patients within the first 6-month period posttransplant,²² with 22% ($n = 5$) of patients above and 30% ($n = 7$) below this range. Examination of the AUC₆₋₁₂ to the AUC₀₋₁₂ suggested that recycling accounted for $34 \pm 10\%$ of the AUC, which is within the previously published range.^{21,22}

The C_{tr} at 12 hours exceeded the range of 1.0–3.5 mg/L that is recommended in transplant patients,²² with 22% ($n = 5$) above this target. The $t_{\max}$ varied from 0.5 to 5 hours, severely limiting applicability of shortened plasma collections for AUC determination.

The MPA Cl_r represented 2% of the Cl/F, which is consistent with previous reports.²¹ As suggested previously, the clearance of MPA is primarily the result of systemic metabolism to MPAG.¹¹ The Cl_r of MPA was 5.77 ± 5.80 mL/min, which was 9% of the CrCl in our patients.

MPAG Pharmacokinetics

The MPAG pharmacokinetic results are reported in Table 1. A calculated AUC₀₋₁₂ ratio of MPAG to MPA resulted in a metabolic ratio of 8.67 ± 5.57 , less than previously reported in renal transplant recipients.²³

The renal clearance of MPAG was 33.7 ± 34.9 mL/min, representing 40% of the CrCl. The kidneys contributed to the elimination of 97% of the MPA dose, primarily through excretion of MPAG. The amount of MPAG in the urine over the 0- to 12-hour interval (513 ± 285 mg) was more than the amount in the 12- to 24-hour interval (378 ± 257 mg; $p = 0.017$). The Cl_r was also greater in the 0- to 12-hour (33.7 ± 34.9 mL/min) versus 12- to 24-hour dosing interval (28.4 ± 36.9 mL/min; $p = 0.0043$).

Unbound Pharmacokinetics

Our data showed that 1.0% and 13% of MPA and MPAG, respectively, were unbound in the plasma. Since the unbound MPAG was less than that reported previously,²¹ we performed studies with MPA and/or MPAG spiked heparinized plasma.¹⁷ The plasma that was spiked separately demonstrated similar unbound percentages to those found in our ANCA patient data; the combination of drug and metabolite resulted in an increase in unbound percentage of MPA and MPAG. This may be suggestive of competitive binding to albumin, as has been reported previously.²⁴

Since the normal percentage of unbound MPA is 2%, if one aims for a total MPA Ctr of 1.0–3.5 mg/L, then an unbound target would be 0.02–0.07 mg/L.²¹ Likewise, if suggested total AUC goals are 30–60 mg•h/L, then unbound AUC goals would be 0.6–1.2 mg•h/L. Mean unbound Ctr levels were 0.04 ± 0.06 mg/L (consistent at both the 12- and 24-h time points), with 5 patients exceeding the range and 13 patients below the range; this resulted in only 22% of all patients falling within the targeted kidney transplant range. With regard to unbound AUC, the mean exposure was greater than the upper range of 1.2 mg•h/L in only 1 patient, but was less than the targeted range in 15 patients.

Regression Results

The multiple regression model for MPA Cl/F revealed that race and weight contributed: ranked Cl/F = $-11.766 + 0.2035(\text{wt}) + 4.9578(\text{race})$; R^2 41.8%; $p = 0.005$. The AUC₆₋₁₂ showed the following relationship: $\text{Ln MPA AUC}_{6-12} = 3.706 - 0.0094(\text{CrCl})$; R^2 36.86%; $p = 0.0021$. In analysis of MPA Clr, the AUC₆₋₁₂ was the only significant contributing variable: ranked MPA Clr = $30.2674 - 6.2733(\text{Ln AUC}_{6-12})$; R^2 33.2%; $p = 0.004$. Regression assessment of the predictors for unbound MPA clearance indicated that CrCl and age were important: Ranked $\text{Cl}_{\text{unb}} = 16.055 + 0.0601(\text{CrCl}) - 0.1994(\text{age})$; R^2 52.3%; $p = 0.0013$. MPAG Clr analysis showed that race and prednisone dose contributed. $\text{Ln MPAG Clr} = 2.6645 + 1.1799(\text{race}) - 0.3041(\text{ranked prednisone dose})$; R^2 88.0%; $p = 0.014$.

Comparison Between Groups Based on Clinical Laboratories

The differences in pharmacokinetics by clinical grouping of UP:Cr (<500 vs ≥ 500) and CrCl (<60 mL/min vs ≥ 60 mL/min) were assessed (Table 2). There was a considerable distribution of CrCl across the population (low 18.3 mL/min, high 182 mL/min). Since MPAG is eliminated via the renal route, reductions in renal elimination would be predicted to have more direct effects on MPAG, with secondary effects on MPA due to potential enhanced MPA AUC₆₋₁₂, reflective of enterohepatic recycling (Table 2).

The MPA Ctr values were 3-fold higher in patients with reduced CrCl compared with those who had higher CrCl (6.88 ± 6.8 vs 2.72 ± 1.81 , respectively; $p = 0.030$). The AUC₆₋₁₂ demonstrated 2 to 3-fold higher values in low versus high CrCl grouping (35.9 ± 27.0 vs 16.7 ± 8.8 mg•h/L, respectively; $p = 0.015$). The MPA AUC₀₋₁₂ was 2-fold greater in the low versus high CrCl grouping (95.0 ± 66.9 vs 52.5 ± 22.8 mL/min, respectively; $p = 0.023$). The MPA AUC₀₋₁₂ unbound values were significantly higher in the low CrCl group (1.29 ± 0.608 vs 0.592 ± 0.562 mg•h/L; $p = 0.032$), suggesting the presence of more pharmacologically active drug. The MPA Cl_{unb} was 3-fold reduced in the low CrCl group, with a trend toward statistical significance, which may be suggestive of reduced metabolism and/or CrCl. While the Clr MPAG was not significantly different between groups, the MPAG AUC₀₋₁₂ was enhanced 2-fold in the low CrCl patient group (959 ± 664 vs 404 ± 336 mg•h/L; $p = 0.014$).

UP:Cr was selected as a clinical variable secondary to the high plasma protein binding characteristics of MPA and MPAG. To enable at least 5 observations per group, a cut-point of 500 mg/day was selected. None of the pharmacokinetic parameters was statistically significant

between the high and low UP:Cr grouping. Only 4 patients had UP:Cr greater than 1.0 g/day, preventing a comparison that may be more likely to be clinically relevant.

Discussion

While descriptions of the pharmacokinetics of MPA in patients who have undergone kidney transplant are abundant, there is a paucity of data on the pharmacokinetics in autoimmune diseases that affect the kidney. Our study was conducted to comprehensively evaluate the pharmacokinetics of MPA and MPAG after chronic therapy in patients with ANCA-associated vasculitis. Additionally, we wanted to understand the relevance of clinical and demographic variables in predicting pharmacokinetic parameters. CrCl was positively predictive for MPA Cl_{unb} and negatively predictive for MPA AUC_{6-12} . Race was found to positively predict both MPA Cl/F and MPAG Cl_r , whereby nonwhite patients had higher clearance values, suggesting an influence on both metabolism and Cl_r . Prednisone dosage was negatively associated with MPAG Cl_r , suggesting an influence on active renal secretion. Unfortunately, the influences of UP:Cr and serum albumin on pharmacokinetic variables were not able to be fully assessed secondary to limited distribution of UP:Cr and relatively conserved values of serum albumin. A study of MPA use in patients with lupus nephritis showed that at a UP:Cr of 1 g/day or more, Cl_r and AUC_{0-12} were significantly reduced and Cl/F was significantly increased.¹⁷ We previously reported higher MPA Cl_{unb} and MPAG Cl_r levels in patients with lupus nephritis patients with serum albumin levels less than 4 g/dL versus those with levels greater than or equal to 4 g/dL.¹⁷

CrCl significantly affected the pharmacokinetics of MPA and MPAG in ANCA-associated vasculitis. Although MPA itself is not highly eliminated by the kidneys, exposure was markedly enhanced in the low CrCl grouping, with dosing interval (AUC_{0-12}), enterohepatic recycling (AUC_{6-12}), and unbound ($AUC_{0-12unb}$) exposures being significantly greater. Since MPAG is primarily eliminated by renal excretion, reductions in CrCl may predispose patients to higher concentrations of MPAG, which, through recycling, can increase systemic exposure to MPA. These results suggest that patients with diminished kidney function can reach targeted MPA exposure ranges with lower dosages, thus minimizing adverse events. Lower unbound MPA (eg, AUC) would not be predicted to be increased through a purely restrictive clearance mechanism, and our patients were not hypoalbuminemic; hence, our data may suggest the influence of additional factors affecting plasma concentrations in patients with glomerular kidney diseases. Assessment of MPA Cl_r values showed a consistent 2- to 3-fold higher value in patients with CrCl less than 60 mL/min compared with those with CrCl greater than 60 mL/min. When we performed a post hoc analysis of variance to evaluate the differences in pharmacokinetics based on CrCl groupings, we found that significant differences in Cl_r , recycling AUC , unbound AUC , and unbound clearance were all demonstrated between the patients with chronic kidney disease stage 3/4 versus stage 1 group. Only unbound clearance was found to also be significant between the stage 3/4 versus stage 2 group.

The pharmacokinetics of MPA in patients with ANCA vasculitis are comparable with pharmacokinetics in renal transplant patients, with the exception of Cl/F , which is about 2-fold greater in patients with vasculitis. Reasons for enhanced Cl/F can include increased systemic metabolism secondary to upregulated glucuronidation, increased MPA unbound fraction, or enhanced renal excretion. Regarding enhanced glucuronidation, patients receiving concurrent steroids (enzyme inducers) had similar Cl/F estimates as patients who were not receiving steroids (data not shown). We are currently evaluating the contribution of enhanced catalysis polymorphisms in the uridine diphosphate glucuronosyltransferases (UGTs) as factors altering MPA clearance. The metabolic ratio, a reflection of metabolite to parent AUC , was 8.67 ± 5.57 in our study, considerably less than the 25.6 ± 8.7 that was previously reported in kidney transplant recipients.²³ The unbound fraction was relatively normal (~1%) in our patients, as

they had essentially normal serum albumin concentrations (3.6–5.2 g/dL). Enhanced renal clearance can result from increased CrCl, loss of highly protein-bound drugs with urinary protein, or enhanced secretory transport mechanisms. Our patients with ANCA vasculitis had a mean CrCl of 84 mL/min, with a range between 18 and 182 mL/min. Although renal elimination of MPA is limited, enhanced CrCl could result in increased clearance secondary to renal clearance of the polar metabolite MPAG. Enhanced renal clearance secondary to loss of the highly protein bound MPA with the urinary protein could also account for an increase in Cl/F. However, when we evaluated Clr between patients with UP:Cr less than 500 mg/day and those with UP:Cr greater than or equal to 500 mg/day, the results were similar. The magnitude of differences in Clr between UP:Cr groups may have been underappreciated, based on our selected cut-point. MPAG is a substrate for MRP2, an efflux transporter found on the luminal surface of the proximal tubule. Theoretically, single nucleotide polymorphisms (SNPs) in this transport gene can result in enhanced activity and could increase the renal excretion of MPAG, limiting the effect of recycling.

Renal transplant recipients, similar to our ANCA vasculitis patients, generally have reductions in CrCl. A previous study used a multivariate analysis and demonstrated that 24% of the MPA Cl/F could be explained by proteinuria (yes/no), glomerular filtration rate, and diabetes mellitus.²⁵ Unfortunately, the range of proteinuria required to designate a yes versus no categorization was not reported. Our regression data showed that CrCl was predictive for both Cl_{unb} and AUC_{6-12} . Previous data on lupus nephritis from our laboratory showed that 51% of MPA Cl/F could be explained by CrCl and serum albumin, 2 readily measured clinical laboratory measures.¹⁷ The contribution of race to MPA Cl/F in our vasculitis patients requires assessment of genotype as a confounding variable, as genomic effects have been shown to influence the pharmacokinetics of MPA.^{19,20,26} CrCl would generally be predicted to contribute little to MPA Cl/F, secondary to the low percentage of MPA (1–3%) that is normally excreted by the kidneys. Hence, nonrenal clearance, through metabolism of MPA to MPAG, would comprise the largest bulk of the Cl/F for MPA. Our regression analyses demonstrated that AUC_{6-12} was the only significant predictor of MPA Clr, demonstrating an influence of MPA plasma concentration on Clr. The regression models are important, as they provide insights into the mechanisms that may underlie the alterations in pharmacokinetics seen in disease states such as ANCA-associated vasculitis. This is particularly important, since there is a paucity of published research on medication off-label disease groups, whereby there can be extensive variations in medication handling versus in the diseases for which the drugs were FDA approved.

Unlike our ANCA vasculitis patients, our previous report on MPA pharmacokinetics in patients with lupus nephritis showed higher UP:Cr and lower serum albumin and CrCl.¹⁷ The key differences in pharmacokinetics of MPA and MPAG between these studies included enhanced MPA MRT, MPA Clr, metabolic ratio ($MPAG_{AUC}/MPA_{AUC}$), unbound MPAG %, and MPA Cl/F_{unb} ; reduced MPA AUC_{0-12} , MPA AUC_{6-12} , MPAG Clr, MPA Cl_{unb} , and MPA AUC_{unb} ; and normal unbound MPA % in the ANCA vasculitis versus lupus nephritis population. These data generally demonstrate lesser MPA exposure in patients with ANCA-associated vasculitis as opposed to those with lupus nephritis. While lower MPA dosages in the ANCA vasculitis populations could reflect reduced exposure, our data were dose-normalized to eliminate the dose effect. The effects of SNPs in UGT enzymes requires assessment in these autoimmune diseases, especially since environmental exposure is thought to play a role in their etiology and since the UGT enzymes play a role in the body's natural defense against environmental toxins. Additionally, the role of inflammation in MPA pharmacokinetics in autoimmune diseases requires evaluation as a potential disease component that may modify drug metabolism and transport.

While we report the contribution of CrCl to MPA clearance and exposure in a model of ANCA vasculitis, there are some limitations to our research. As noted previously, our patients had preserved serum albumin concentrations, preventing full assessment of the contribution of reductions in serum albumin on clearance. Similarly, since only 4 patients in our dataset had UP:Cr of approximately 1 g/day and none had nephrotic-range proteinuria (UP:Cr >3.5 g/day), the full contribution of UP:Cr to clearance may actually be underrecognized. Future analyses of our data include assessment of the contribution of genotype for drug-metabolizing enzymes and transporters on clearance and outcomes, as well as the analysis of the contribution of Ctr and AUC to patient outcomes. Our studies on autoimmune-related kidney diseases are important, as they provide a framework to understand the contributions of disease-related and -unrelated factors to MPA exposure. A goal of our future work is to better define appropriate MPA concentration or exposure targets for patients with ANCA-associated vasculitis.

Approaches to comprehensively evaluate the influence of clinical and demographic factors on MPA pharmacokinetics are needed to begin to identify variables that could be used to individualize treatment strategies for patients with ANCA-associated vasculitis.

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Figure 1.

Plasma concentration versus time profile for mycophenolic acid (MPA) and its glucuronide metabolite (MPAG) after chronic dosing (every 12 hours) in one patient.

Table 1**Pharmacokinetic Parameters in Patients with ANCA-Associated Vasculitis^a**

MPA	
t _{max} (h)	1.46 ± 1.24
C _{max} (mg/L) ^b	21.5 ± 20.3
Ctr ₁₂ (mg/L) ^b	3.99 ± 4.32
lambda (h ⁻¹)	0.07 ± 0.04
MRT (h)	27.2 ± 36.2
AUC _{MPA0-12} (mg•h/L) ^b	65.4 ± 44.4
AUC _{MPA6-12} (mg•h/L) ^b	22.6 ± 18.3
Cl/F (mL/min) ^c	288 ± 154
Clr ₀₋₁₂ (mL/min) ^c	5.77 ± 5.80
Ae ₀₋₁₂ (mg)	13.6 ± 12.2
% unbound	1.02 ± 0.66
MPAG	
t _{max} (h)	2.51 ± 1.44
C _{max} (mg/L) ^b	74.3 ± 58.9
Ctr ₁₂ (mg/L) ^b	35.1 ± 32.3
lambda (h ⁻¹)	0.07 ± 0.04
AUC _{MPAG0-12} (mg•h/L) ^b	573 ± 515
MPAG:MPA ratio	8.67 ± 5.57
Clr ₀₋₁₂ (mL/min) ^c	33.7 ± 34.9
Ae ₀₋₁₂ (mg)	513 ± 285
% unbound	12.9 ± 7.0
Unbound MPA	
C _{max} (mg/L) ^b	0.22 ± 0.24
Ctr ₁₂ (mg/L) ^b	0.04 ± 0.06
AUC _{MPA0-12} (mg•h/L) ^b	0.76 ± 0.64
Cl/F (L/min) ^c	37.0 ± 29.6

Ae = amount excreted in the urine; ANCA = antineutrophil cytoplasmic antibody; AUC = area under the plasma concentration–time curve; C_{max} = maximum plasma concentration; Cl/F = oral clearance; Clr = renal clearance; Ctr₁₂ = trough plasma concentration at 12 hours; MPA = mycophenolic acid; MPAG = mycophenolic acid glucuronide; MRT = mean residence time; t_{max} = time to C_{max}.

^a Mean ± SD.

^b Normalized to a 1000-mg dose.

^c Scaled to a body size of 70 kg, using 0.75 power.

Table 2

Clinical Grouping of Patients and Pharmacokinetics^a

Pharmacokinetic Parameter	Status		p Value
	<60 mL/min	≥60 mL/min	
Pts., n	7	16	
MPA			
% unbound	0.9 ± 0.7	1.1 ± 0.7	0.598
Ctr ₁₂ (mg/L) ^b	6.88 ± 6.79	2.72 ± 1.81	0.030
AUC ₀₋₁₂ (mg•h/L) ^b	95.0 ± 66.9	52.5 ± 22.8	0.023
AUC ₆₋₁₂ (mg•h/L) ^b	35.9 ± 27.0	16.7 ± 8.8	0.015
Cl/F (mL/min) ^c	210 ± 86.7	323 ± 67	0.109
Cl _{r0-12} (mL/min) ^c	3.36 ± 3.07	6.77 ± 6.48	0.340
Cl _{unb} (mL/min) ^c	15,928 ± 6376	43,539 ± 31,045	0.067
AUC _{0-12unb} (mL/min) ^b	1.29 ± 0.608	0.592 ± 0.562	0.032
MRT (h)	36.9 ± 35.9	23.4 ± 36.8	0.452
MPAG			
AUC ₀₋₁₂ (mg•h/L) ^b	959 ± 664	404 ± 336	0.014
Cl _{r0-12} (mL/min) ^c	21.8 ± 20.2	38.9 ± 39.1	0.249
MPAG AUC ₀₋₁₂ /MPA AUC ₀₋₁₂	10.7 ± 6.19	7.77 ± 5.24	0.278
UP:Cr			
Pts., n	<500 mg/day 15	≥500 mg/day 6	
MPA			
% unbound	0.99 ± 0.65	1.21 ± 0.78	0.516
Ctr ₁₂ (mg/L) ^b	3.07 ± 1.79	6.56 ± 7.87	0.381
AUC ₀₋₁₂ (mg•h/L) ^b	55.8 ± 22.3	84.5 ± 80.6	0.791
AUC ₆₋₁₂ (mg•h/L) ^b	18.9 ± 9.18	32.2 ± 32.6	0.153
Cl/F (mL/min) ^c	300 ± 163	285 ± 165	0.970
Cl _{r0-12} (mL/min) ^c	5.47 ± 6.08	7.31 ± 6.23	0.569
Cl _{unb} (L/min) ^c	43.5 ± 33.5	19.7 ± 12.5	0.145
AUC _{0-12unb} (mg•h/L) ^b	0.82 ± 0.74	1.25 ± 0.82	0.186
MRT (h)	24.2 ± 37.8	43.4 ± 36.8	0.186
MPAG			
AUC ₀₋₁₂ (mg•h/L) ^b	467 ± 366	860 ± 798	0.733
Cl _{r0-12} (mL/min) ^c	28.1 ± 19.5	45.9 ± 62.0	0.791
Metabolic ratio	8.46 ± 5.57	9.95 ± 6.48	0.340

AUC = area under the plasma concentration–time curve; Cl/F = oral clearance; Cl_r = renal clearance; CrCl = creatinine clearance; Ctr₁₂ = trough plasma concentration at 12 hours; MPA = mycophenolic acid; MPAG = mycophenolic acid glucuronide; MRT = mean residence time; unb = unbound; UP:Cr = urinary protein to creatinine excretion ratio.

^a Mean ± SD, unless otherwise indicated.

^b Normalized to a 1000-mg dose.

^c Scaled to a body size of 70 kg, using 0.75 power.